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Physiology of oxygen breathing in pilots: a brief review

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Physiology of oxygen breathing in pilots: a brief review

Abstract

This non-exhaustive survey presents literature describing some effects of breathing oxygen partial pressures between normoxic 21 kPa and normobaric hyperoxic 100 kPa (160 to 760 Torr). Absorption atelectasis is a concern when the fraction of oxygen (F_IO_2) in the breathing gas is high, but for all other risks, oxygen partial pressure (PO_2) is the variable of interest. Gas transport and oxygen delivery in people with healthy lungs is not improved by elevated alveolar PO_2. Atelectasis (absorption injury) is of concern if F_IO_2>80% and small airways (or eustachian tubes or sinus ostia) are blocked. Absorption becomes faster as altitude increases. Pulmonary oxygen toxicity and direct oxidative injuries are improbable in flight -- No pulmonary oxygen toxicity has been found when PO_2 < 55 Pa (418 Torr), symptoms reported for PO_2 of 75 kPa (520 Torr) were reported after 24-hours' exposure, and the earliest signs reported at PO_2 of approximately 100 kPa (760 Torr, 100% oxygen at sea level) occurred after 6 hours. However, aviators who are treated for suspected decompression sickness run the risk of pulmonary oxygen toxicity. Other effects of elevated PO_2 include constriction of blood vessels, changes in blood pressure control, and poor response to low blood sugar. Finally, the near zero humidity of the gas stream in which oxygen is delivered to the air crew may predispose susceptible individuals to bronchoconstriction.

Introduction

Although the oxygen supply to the brain and tissues must be maintained, an excess of oxygen can be dangerous. Hypoxia represents a more immediate risk to pilots at altitude than does hyperoxia, but “more” is not necessarily “better” when oxygen is concerned. This brief review addresses the risks of oxygen breathing for pilots.

Adverse effects of oxygen (O_2) can be grouped into physical effects (i.e., atelectasis), toxic effects, and deleterious other effects of oxygen (e.g., otherwise inappropriate vasoconstriction). An additional physical factor of oxygen delivery, inspired humidity, can exacerbate the physical and toxic responses. The variable of importance for atelectasis is the fraction of oxygen in the inspired gas. For **all** other effects, the oxygen partial pressure (PO_2) is the critical quantity. PO_2 is both the driving force for oxygen transfer (both into the blood in the lungs and to tissue in the periphery) and a close approximation of the chemical activity of oxygen.

In gas, PO_2 is the pressure that would prevail if all other gas species were removed. It is calculated as the fraction of oxygen present (number of oxygen molecules per total number of molecules in a given volume) multiplied by the ambient pressure. PO_2 is thus an index of the amount of oxygen available for any chemical process.

In liquid, PO_2 is a measure of dissolved oxygen, again an indicator of the amount of oxygen available for chemical processes. If a gas phase and a liquid phase are in contact with each other, oxygen will move between the two until they are equilibrated. When there is no net transfer between the phases, the PO_2 in the liquid is said to equal that in the gas. Thus, PO_2 in a liquid is defined as the PO_2 in a hypothetical gas in equilibrium with the liquid. PO_2 differences, for example, blood to tissue or alveolar gas to pulmonary capillary blood, are the driving force for (diffusive) oxygen transfer.

Gas exchange

The rate of oxygen delivery to the tissues and brain is a function of local capillary oxygen partial pressure and blood flow, and the local oxygen partial pressure, representing the oxygen dissolved in the blood, is in equilibrium with the hemoglobin oxygen saturation.

Ideal lungs: Consider first an “ideal” lung in which alveolar gas is homogenous, blood flow to the lungs is well-distributed, and thus arterial oxygen partial pressure (P_aO_2) equals alveolar oxygen partial pressure (P_AO_2). P_AO_2 is related to but always less than the PO_2 of inspired gas. The alveolar gas equation (Fenn et al., 1946; Taylor et al., 1989) is derived from the premise that at steady state, the amount of inert gas inhaled

equals the amount of inert gas exhaled. If inhaled gas contains no carbon dioxide (CO_2), the result is that at steady state,

$$P_AO_2 = P_IO_2 - (P_ACO_2/R) \cdot [1\text{-}F_IO_2 (1-R)] \quad [1]$$

$$= P_IO_2 - [V'CO_2/ (V'_A \cdot R)] \cdot (P_T - P_w) \cdot [1 - F_IO_2 (1-R)] \quad [2]$$

$$= P_IO_2 - [V'O_2/ V'_A] \cdot (P_T - P_w) \cdot [1 - F_IO_2 (1-R)] \quad [3]$$

where P_ACO_2 is alveolar carbon dioxide partial pressure, F_IO_2 is inspired oxygen fraction, R is respiratory ratio $V'CO_2/(V'O_2)$, $V'CO_2$ is the rate of CO_2 release into lung gas from the blood, $V'O_2$ is the rate of oxygen uptake from lung gas into the blood, P_T is ambient (total, cabin) pressure, P_w is the partial pressure of water vapor in air saturated at body temperature, and V'_A is the rate of alveolar ventilation, that is, the volumetric flow of fresh gas to the gas exchange zones of the lungs. All volumes here are expressed at standard temperature and pressure. All fractions are expressed on a dry gas basis, i.e., where $FO_2 + FCO_2 + F_{inert\ gas} = 1$, with the fraction of water vapor not included in the summation.

If the gas breathed is 100% oxygen or if R = 1,

$$P_AO_2 = P_IO_2 - P_ACO_2 \quad [4]$$

$$= F_IO_2 \cdot (P_T - P_w) - P_ACO_2 \quad [5]$$

$$= P_IO_2 - [V'CO_2/ V'_A] \cdot (P_T - P_w) \quad [6]$$

This equation in the several forms given above indicates that i) inhaled O_2 is diluted by CO_2 and by water vapor in the lungs; ii) that the amount of dilution with CO_2 depends on the ratio of metabolic rate ($V'O_2$) to the volume and rate of breathing (V'_A); and iii) that ambient pressure and inhaled oxygen fraction have effects individually, not only as the product $P_IO_2 = F_IO_2 \cdot P_T$. Both P_ACO_2 and P_w are independent of ambient pressure; from equation 5 it is clear that P_ACO_2 begins to infringe upon P_AO_2 if P_T is low.

Hemoglobin oxygen saturation S_aO_2 is a direct function of PO_2 in the blood. However, the sigmoidal hemoglobin dissociation curve determines that no more oxygen can be taken up by hemoglobin once PO_2 exceeds about 100 Torr. For a person with a normal hemoglobin concentration, approximately 20 mL (STPD) of oxygen is bound to hemoglobin in each 100 mL of arterial blood for $P_AO_2 \geq 100$ Torr.

If P_AO_2 is greater than 100 Torr only the amount of oxygen dissolved in blood can increase. The capacity for oxygen in solution in 100 mL of blood is 0.003 mL (STPD)/Torr. A five-fold increase in inhaled oxygen partial pressure leads to less than a 10% increase in the total volume (STP) of oxygen, dissolved and bound, contained in arterial blood.

Hemoglobin oxygen saturation affects CO_2 transport in the blood (the Haldane effect), with high hemoglobin oxygen saturation decreasing the sequestration of CO_2 in the blood and thus slightly increasing local PCO_2. PCO_2 affects the hemoglobin saturation curve (the Bohr effect), with decreased PCO_2 increasing the affinity of hemoglobin for oxygen, and thus slightly decreasing the local PO_2 for a given oxygen content. In someone with healthy lungs, the practical effects of hyperoxia on gas exchange are minimal, particularly because the effects tend to counteract each other.

Heterogeneous ventilation: Not all regions of the lung receive the same fraction of the air flow or of the blood flow. Each small region of the lung (acinus) has its own acinar PO_2 and its own fraction of blood flow which equilibrates with the acinar gas. Regional pulmonary blood flow is sensitive to regional PO_2 and PCO_2. Particularly, blood vessels delivering blood to a region in which the PO_2 is low constrict, teleologically to redirect the blood to better-ventilated acini. When P_IO_2 increases, even acini with low air flow see an increase in local P_AO_2, and the local “hypoxic pulmonary vasoconstriction” relaxes, causing a more-uniform distribution of blood flow in the lung. This is coupled with better gas exchange in those acini, increasing the effective surface area for gas transfer in the lung and reducing the presence of those in which gas exchange was occurring but poorly. If the mismatch of ventilation (air flow) and perfusion (blood flow) in the lungs is sufficiently disturbed to impact oxygenation, hyperoxia can improve oxygenation status. This is one of the main bases for clinical use of elevated oxygen partial pressures in patients. Unfortunately, zones of low ventilation are prone to closing completely if they contain 100% oxygen and the airway closes.

If some regions of the lung receive no ventilation because of airway closure and/or atelectasis, any blood passing through those zones (“shunted”) will have the PO_2 of venous blood. The P_aO_2 in the arterialized blood entering the left side of the heart is a volume average of the PO_2 from all zones of the lung. If the shunt fraction (fraction of total blood flow not undergoing gas exchange in the lungs) is large, systemic arterial PO_2 will be depressed, and provision of even 100% oxygen in inspired gas will not increase it. S_aO_2 corresponds to systemic P_aCO_2.

Summary: When the lungs are healthy, increasing P_AO_2 above about 100 Torr cannot significantly improve gas exchange or oxygen transport. Clinical use of higher PIO2 is justified if regions of the lungs are poorly ventilated. In that case, increased P_AO_2 will increase S_aO_2 as long as the small airways in the poorly ventilated regions stay open,

but may decrease it if they do not. If blood flows through non-ventilated regions of the lungs, P_AO_2 > 100 Torr will not increase S_aO_2.

Adverse physical effects of oxygen fraction: atelectasis

Oxygen is readily absorbed into tissues, because tissue metabolism consumes it. Thus, if a volume of gas that contains oxygen is enclosed in a poorly-ventilated gas space in the body, the volume of contained gas will shrink as molecules of oxygen leave the space. If the gas is room air, the volume can shrink only to about 80% of its initial size, leaving nitrogen behind. However, if the gas is 100% oxygen, the entire volume can be absorbed, causing, for example, the disappearance of an oxygen gas bubble, a reduction of pressure in a rigid space sufficient to draw liquid from the surrounding tissues, or the collapse of a pliant structure to the point where the surrounding tissues touch.

Gas bubbles: Because oxygen bubbles are totally reabsorbed, oxygen prebreathing before decompression provides a degree of protection against decompression sickness. Although bubbles may form in blood and tissues as a result of tissue supersaturation, normal metabolism will clear them fairly rapidly. (They may begin a cascade of adverse effects while they last, but that is a different topic.)

Rigid space: When a large fraction of oxygen is trapped in the paranasal sinuses or in the middle ear, the resulting decrease in pressure as the gas is absorbed causes acute pain, fluid leakage from tissue into the gas space, and, in the case of the ear, eardrum deformation and altered hearing. The oxygen absorption effectively causes an ear or sinus "squeeze" several hours after the exposure. (Because this is a common after-effect of breathing on Draeger 100% oxygen rebreather underwater breathing apparatus (UBA), Navy divers know the phenomenon as “Draeger Ear”. Medical literature may call it aural atelectasis or middle ear absorption syndrome.)

Pliant structure: When gas with a large fraction of oxygen is trapped in a region of the lung, that region will collapse as the oxygen is absorbed, causing absorption atelectasis. Symptoms of atelectasis include cough and a sense of chest tightness or the inability to inhale deeply, a feeling that is similar to that of lying on one's chest on a hard surface. This is a common side-effect of surgery when patients are ventilated with high oxygen-fraction gas (Dugan and Kavanagh, 2005). Atelectic regions of the lung cannot contribute to gas exchange and can be hard to reinflate.

Absorption atelectasis occurs only if parts of the lungs are poorly ventilated or not ventilated at all because of closure of small airways. Airway closure often occurs when lung gas volume is reduced, for example, by a restrictive vest (Caro et al., 1959), or

when blood is translocated into the chest, for example, during head-out water immersion (Balldin et al, 1971) or on inflation of an anti-gravity ensemble (Grönkvis et al., 2003). For some individuals, airway closure is normal in a supine posture (Webb et al., 1993; LeBlanc et al, 1970), or at the base of the lungs even when seated (LeBlanc et al, 1970), because of movement of blood into the chest or compression of the lowest parts of the lungs by the abdomen. Occasional deep breaths can reopen closed airways. Alveolar stretch also renews the film of lung surfactant, the detergent-like substance that helps to stabilize alveoli by reducing surface tension, on alveolar membranes (Duggan and Kavanagh, 2005). Thus, the inability to take deep breaths promotes atelectasis.

Altitude increases the need for anti-closure maneuvers like deep breaths. As total pressure decreases, a volume of oxygen represents fewer molecules than it does at ground level, and the rate of volumetric absorption of oxygen behind closed airways increases (Robertson and Farhi, 1965).

Even in healthy people, atelectasis can remove significant fractions of the lungs from gas exchange. For example, Balldin et al. (1971) found that two hours of water immersion to the chin reduced vital capacity (the volume of gas between maximum inspiration and maximum expiration, that is, the changeable lung gas volume) by about 8% when subjects breathed air, but by 22% when the subjects breathed 100% oxygen. Atelectasis during and after surgery can be severe enough to cause arterial oxygen desaturation (Hedenstierna, 2010). Rothen et al. (1995b) documented an effective average shunt fraction of 9.8% of cardiac output in six patents ventilated with 100% oxygen, but an average shunt fraction of only 3.2% in six people ventilated with 30% oxygen.

Shunt fraction is the fraction of the cardiac output (blood flow from the heart) that effectively bypasses gas exchange in the lungs; a shunt fraction of 10% means that 90% of the blood is oxygenated, probably to 100% saturation, but 10% is not. The arterial blood leaving the heart is a mixture of the two. For example, if the content of oxygen in the blood leaving the lungs is 20 mL(STPD) /100 mL and that in the mixed venous blood reaching the lungs is 15 mL/100 mL, with a 10% shunt the arterial content will be (0.9 x 20) + (0.1 x 15) = 19.5 mL/100 mL. Paradoxically, high oxygen fraction in the breathing gas sometimes can reduce the amount of oxygen available to the brain and tissues by promoting atelectasis, and hence, shunt.

Only small fractions of nitrogen need to be present in breathing gas to prevent total alveolar collapse. Gas with 80% or less oxygen has been suggested as sufficient to significantly reduce atelectasis after surgery (Edmark et al., 2003), with the incidence and severity of atelectasis after anesthesia similar for 80% or 30% oxygen. Another study showed that atelectasis can be cleared in the long term by lung re-inflation with

40% oxygen, while it rapidly reappeared after similar re-inflation with 100% oxygen (Rothen et al., 1995a). In one individual, 5% nitrogen (95% oxygen) was shown to prevent atelectasis at altitude (DuBois et al., 1966), but a case study of one individual cannot be generalized very far.

Recommendations: To prevent absorption atelectasis in flight, the fraction of oxygen in the breathing gas should be as low as possible commensurate with maintaining P_AO_2. Further, pilots should be encouraged (and able) to take very deep breaths periodically, particularly at high altitude.

Adverse effects of elevated PO_2

1. Oxygen toxicity

Central nervous system (CNS) oxygen toxicity produces neurological symptoms, the most severe of which is convulsion. It does not occur under normo- or hypobaric conditions. The threshold for any concern in diving (submerged) is inspired an PO_2 of 1.3 atm (approximately 130 kPa; 990 Torr) (Naval Sea System Command, 2016). In dry exposures (treatment chambers) the seizure rate with inspired PO_2s of 2 to 2.5 atm (approximately 200 to 250 kPa, 1580 to 1980 Torr) for 60 to 120 minutes is only 0.03% (Hampson and Atik, 2003).

Pulmonary oxygen toxicity is a clinical entity that begins with airway symptoms and some degradation of pulmonary function. If left unchecked, it can progress over the course of hours or days of continuous exposure, depending on the PO_2, to serious lung injury and even death. Data (Clark and Lambertsen, 1971) indicate that PO_2 of 0.55 atm is safe for multiple days of continuous exposure while 0.75 atm is not; there have been no measurements between those values. The nervous system is implicated in pulmonary oxygen toxicity after exposure to high, hyperbaric PO_2s (>200 kPa; 1520 Torr) (Demchenko et al., 2007).

Symptoms of pulmonary oxygen toxicity are initially those of a tracheo-bronchitis: a burning or aching sensation in the central chest that is made worse by rapid or deep inhalation; cough; chest tightness, breathlessness, or shortness of breath; and sometimes hoarseness. Those with even low levels of pulmonary oxygen toxicity also often report unreasonable fatigue and exercise intolerance for up to days after the oxygen exposure. The fatigue is probably not related to pulmonary injury – there is no correlation with any indices of pulmonary function – but rather, a different manifestation of oxygen toxicity.

Pulmonary oxygen toxicity with PO_2 from about 75 kPa (0.75 atm; 570 Torr) to about 160 kPa (1.6 atm) begins in the lungs, with an inflammatory process following the initial oxygen insult (Demchenko et al, 2007). It is somewhat analogous to a sunburn, in that an inflammatory injury follows the initial damage, and that the injury exists before the symptoms and signs are apparent. The first attack, presumably by reactive oxygen species, damages the pulmonary capillary endothelium, that is, the lining of the small gas-transfer blood vessels in the lung. The resulting immune response causes further damage, leading to leaks from the blood into the interstitial spaces (i.e., the spaces between the cells). Lung volume changes caused by interstitial edema are within the error of measurement of vital capacity measurements (Shykoff, 2001), though the fluid cuffing of airways may decrease forced expired volume in 1 s (FEV_1). If the injury progresses, liquid will leak into the alveoli themselves, where alveolar edema can be measured as a decrease of vital capacity. Continued oxygen insult will lead to what amounts to scarring and permanent thickening of the alveolo-capillary membrane as fibrous material is laid down. Continued oxygen exposure can lead to death, an endpoint reached in many animal studies. In one human study, patients with terminal brain damage were ventilated on 100% oxygen until death; after 30 hours, arterial oxygen saturation began a rapid decline (Barber et al., 1970).

Three sets of studies provide evidence that pulmonary oxygen toxicity is related to oxygen partial pressure (PO_2) and not to oxygen fraction (FO_2). 1) Comroe et al. (1945) compared 34 subjects who breathed 100% oxygen at normal atmospheric pressure to ten who breathed 50% oxygen at normal pressure and six who breathed 100% oxygen in an altitude chamber at 18,000 ft (50 kPa [0.5 atm] total pressure). Those for whom inspired PO_2 was 50 kPa had no symptoms regardless of whether the gas was 50% or 100% oxygen, while 30 of 34 for whom PO_2 was 1 atm complained of substernal pain. 2) A hyperbaric chamber exposure to air at 5 atm (PO_2 approximately 1 atm) (Eckenhoff et al, 1987) produced results indistinguishable from those after several studies conducted at atmospheric pressure with 100% oxygen. 3) A series of three underwater exposures to PO_2 = 130 kPa (1.3 atm) (Shykoff, 2005, 2007a, 2007b), one at a total pressure of 130 kPa with 100% oxygen, one at a total pressure of 160 kPa (1.6 atm) with 80% oxygen, and one at a depth of 50 feet with a rebreather UBA that controls to PO_2 = 1.3 atm, produced indistinguishable signs and symptoms of pulmonary oxygen toxicity.

Pulmonary oxygen toxicity was not evident in any of 13 reports of exposures to PO_2 less than or equal to 0.55 atm (Clark and Lambertsen, 1971). Note, though, that although exposure to PO_2 of 50 kPa (0.5 atm; 380 Torr) for 24 hours caused no symptoms in 16 subjects, it may have reduced vital capacity by a meaningful amount in one person, as read and interpreted from the figure in the paper (Comroe et al, 1945).

Inspired PO_2 does not need to be much higher than 55 kPa (0.55 atm; 418 Torr; 8.1 psi) to be toxic to the lungs after prolonged exposures. After 24 hours, PO_2 of 75 kPa provoked symptoms in five of nine subjects . That exposure also caused a meaningful decrease in vital capacity in one or perhaps two individuals, again as read and interpreted from the figure in the paper (Comroe et al., 1945). Pulmonary oxygen toxicity with PO_2 from 83 to 89 kPa (0.83 to 0.98 atm) has been reported by five other groups after exposures of 24 hours or more, as reviewed by Clark and Lambertsen (1971). Since that review, Davis et al (1983) reported evidence of alveolo-capilary leaks after 17 hours' exposure to PO_2 of 95 kPa (0.95 atm). Additionally, Sachner et al. (1975) showed tracheitis and impaired mucociliary transport in 10 subjects after only six hours' exposure to PO_2 of 95 kPa. Pilots at cabin altitude below 18,000 feet who breathe nearly 100% oxygen are exposed to PO_2s that could provoke pulmonary oxygen toxicity, but toxic effects at those PO_2s require exposures longer than a typical sortie.

Exposures to high oxygen fraction with PO_2 less than 55 kPa (0.55 atm, 473 Torr) that is, to 100% oxygen at altitudes greater than 18,000 feet, appear to be free of pulmonary oxygen toxicity, though not of ear and nasal passage effects (Comroe, 1945; Morgan et al., 1963; Herlocher et al., 1964; DuBois et al., 1963). Multi-day exposures to 100% oxygen at low total pressure may cause other problems; at a total pressure of 190 Torr, 17 days' exposure to 100% O_2 provoked symptoms -- perhaps from the altitude -- in some of the 8 subjects participating.

The greatest risk of pulmonary oxygen toxicity for pilots comes from post-flight treatments, whether with normobaric oxygen for a prolonged period (Comroe, 1945; Davis, 1983; Sackner, 1975) or with hyperbaric oxygen (Smerz, 2004; Shykoff, 2008).

2. Increased oxidative stress

Oxidative stress, usually from the action of reactive oxygen species (ROS) in the body, has been associated with many disease states and with the process of aging. The concern that exposure to elevated oxygen levels could increase overall disease risk is valid. However, most, if not all, studies of increased oxidative stress after exposure to oxygen are conducted with 100% oxygen at the laboratory altitude, that is, with P_IO_2 close to 100 kPa (760 Torr). They therefore represent a much higher PO_2 than that encountered by pilots at altitude. The risk of increased oxidative stress for pilots breathing oxygen at altitude is minimal. For those breathing 100% oxygen at low altitude, duration of exposure is probably important, but data are hard to find.

3. Other effects of altered PO_2

Carotid body:

Ventilatory control: Elevated PO_2 depresses some of the functions of the carotid bodies. In cats, arterial PO_2 greater than 200 Torr eliminates carotid body chemoreceptor output (Lahiri and DeLaney, 1975*)*. Elevated PO_2 causes a time lag between changes in arterial blood and the respiratory responses that can occur only after the change communicates across the blood – brain barrier to the central chemoreceptors.

Blood sugar control: The response to hypoglycemia, particularly the release of adrenalin and glucagon that counteract it, has been shown to be depressed in people breathing 100% oxygen at atmospheric pressure (Wehrwein et al., 2010).

Cardiovascular variables: Hyperoxia (100% O_2 at atmospheric pressure) enhances the baroreflex control of heart rate, decreasing heart rate further in response to elevations in blood pressure (Sinski et al., 2014). It also increases the blood pressure response to isometric exercise and to the presence of metabolites in local tissue beds (e.g., post-exercise occlusion) even though lactate production decreases (Houssière et al., 2005).

Hyperoxic vasoconstriction: Elevated arterial PO_2 stimulates systemic vasoconstriction, that is, narrowing of the resistance arteries in the body and brain. This increases blood pressure until reflex systems, primarily those in the carotid body, reduce heart rate to normalize blood pressure. Oxygen delivery to the brain is unaffected, but CO_2 washout may decrease. In other tissues, the diffusion distance for oxygen and CO_2 may increase because fewer capillaries are open. This is a graded effect of oxygen partial pressure; a progressive increase in oxygenation from normal to mildly hyperoxic (transcutaneous PO_2 from 20 to 60 kPa; approx.150 to 460 Torr) causes a progressive increase in vascular resistance and decrease in stroke volume in supine subjects (Bak et al, 2007).

Hyperoxic hyperventilation: One effect of vasoconstriction is a reduction in brain blood flow, which, by slowing the removal of carbon dioxide (CO_2) from the central chemoreceptors, increases respiratory minute ventilation if breathing is unencumbered. At rest, this produces a mild degree of hyperventilation, that is, respiratory minute ventilation high enough to decrease the arterial PCO_2.

Additional mechanisms have been proposed for hyperoxic hyperventilation (Dean et al., 2004). Independent of the mechanism that increases ventilation, though, the central chemoreceptor response to the lowered PCO_2 that results limits the increase in ventilation, and resting P_aCO_2 decreases only slightly (Becker et al., 1996). The hypocapnia is not sufficient to be expected to cause cognitive changes (Otis et al, 1946) or any significant shifts in hemoglobin oxygen affinity in either arterial or venous blood.

Note that the healthy ventilatory response to hypoxia is hyperventilation (Taylor et al, 1989). Equations [4], [5], and [1] indicate that a decrease in P_ACO_2 yields an increase in P_AO_2. An additional advantage is that decreased P_aCO_2 increases hemoglobin affinity for oxygen, permitting higher S_aO_2 for a given PO_2. Since the hyperventilatory response begins when arterial saturation drops, the increased affinity favors loading of oxygen onto arterial blood in the lungs. At the tissue, local CO_2 will still lower the affinity relative to that in arterial blood to improve oxygen delivery to tissues, though perhaps not to normoxic baseline.

During hypoxic exposures as ventilation increases, respiratory CO_2 washout greatly exceeds metabolic CO_2 production, and the respiratory ratio R increases above 1 (Fenn et al., 1946). Once the P_ACO_2 stabilizes at the value corresponding to the new ventilatory rate, the ratio will once again match that of metabolism.

Although hyperventilation can cause symptoms and loss of function, at least some measures of brain performance are normal at P_ACO_2 of 30 Torr (Otis et al., 1946). Mentally functional climbers breathing air on Mt. Everest had P_ACO_2 from 11 Torr at 6050 m down to 7.5 Torr at the summit (West et al., 1983). At high altitude, exercise performance is greatest in those with high hypoxic ventilatory responses (Schoene et al., 1986). It can be argued that adequate brain and tissue PO_2 takes precedence over concerns for low P_aCO_2.

4. Oxygen delivery at low humidity predisposes to increased airway reactivity

All current tactical aircraft deliver breathing gas at near zero relative humidity. Very dry gas is a known airway irritant which can induce bronchoconstriction (that is, narrowing of the large to medium airways as a result of smooth muscle contraction) in susceptible individuals (Stensrud et al., 2006). While personnel with diagnosed asthma are excluded from flight training, objective screening is not standard in the U.S. Navy or U.S. Air Force as it is in other air forces (Schwarz, et. al., 1997). As a result, personnel with asymptomatic reactive airway disease may become pilots. Approximately 7% to 8% of the U.S. population has some form of asthma or reactive airways disease (CDC, 2011). This percentage is not significantly different among the young adults that make up the active duty population (Al-Hazmi, et al., 2007; Bar Dayan, et al., 2004). It would be reasonable to hypothesize that when exposed to the low humidity environment of tactical aviation, susceptible individuals may develop obstructive pulmonary function changes. Bronchoconstriction may manifest as shortness of breath, chest tightness and/or cough. Although this is not an oxygen effect, it may be confused with one, and it potentially contributes to gas trapping in the lung, the first step towards absorption

atelectasis when F_IO_2 is high. Additionally, the drying of mucous membranes predisposes to sinus and middle ear gas entrapment.

Conclusions

1. The composition of alveolar gas <u>at steady state</u> can be estimated using the alveolar gas equation. The variables involved are P_ACO_2 and respiratory ratio R. These are related directly to metabolic rate and alveolar minute ventilation.

2. Absorption atelectasis is a risk for anyone breathing gas with an oxygen fraction in excess of about 80%. Trapped volume decreases faster at altitude than at sea level. Frequent, very deep breaths could be protective of the lungs, and “ear clearing” maneuvers can reduce middle ear problems. These maneuvers should be recommended both at altitude to maintain gas volume and on return to breathing air, to add nitrogen to the spaces.

3. In healthy lungs, no gas exchange advantage is obtained by increasing P_AO_2 above about 150 Torr. As a first approximation, this suggests that the supplied FO_2 should target 190 /P_T, where P_T is in Torr.

4. Toxic chemical effects of oxygen are unexpected if P_IO_2 < 380 Torr (0.5 atm, 50 kPa, 100% O_2 at and above 18,000 ft). (Note point 2: absorption atelectasis IS a risk with 100% O_2 at any altitude.) Toxic effects of oxygen at lower altitudes are not expected unless exposure duration is long, but early, self-correcting problems have been noted after 6 hours with 100% oxygen on the ground.

5. Carotid body chemoreceptor function is decreased by high P_aO_2, and is probably absent when P_aO_2 >200 Torr (100% O_2 below about 28,000 ft). Pilots breathing oxygen at these altitudes may compensate poorly for hypoglycemia. Heart rate and blood pressure control may be altered.

6. Low humidity of breathing gases may provoke bronchoconstriction in susceptible individuals.

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